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ORIGINAL ARTICLE

Relation between Vitamin D Level and Severity of Paclitaxel-Induced Peripheral Neuropathy in Breast Cancer Patients

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ABSTRACT

Background: Vitamin D deficiency may be an easily detected peripheral neuropathy (PN) risk factor that could be resolved prior to treatment to prevent PN, avoid treatment disruptions, and improve treatment outcomes. This study examined the relations between Vitamin D level before therapy and PN severity during weekly paclitaxel treatment. **Subjects and methods:** This prospective study analyzed data from 38 patients enrolled in an observational cohort study to receive sequential weekly adjuvant paclitaxel for breast cancer. After (AC) Anthracyclines (Doxorubicin), cyclophosphamide (Endoxan) based chemotherapy, patients had HER2 enriched, luminal b HER2 positive received both paclitaxel and trastuzumab (Herceptin) monoclonal antibody against HER2. Life Satisfaction Chemotherapy-Induced Peripheral Neuropathy (CIPN20) Questionnaire was assessed at the beginning of treatment and once weekly until the end of the treatment, we added nerve conduction study (NCS) nerve conduction velocity (NCV) for better assessment. CIPN was assessed by Adapted NCI Common Terminology Criteria for Adverse Events (CTCAE) version 6.0 **Results:** There was a significant relationship type and grade of peripheral neuropathy. With an area under the curve of 0.864, specificity of 83.3%, sensitivity of 80%, positive predictive value of 84.2%, negative predictive value of 78.9%, and overall accuracy of 81.6%, a vitamin D cutoff of 30.75 ng/ml was effective in predicting the occurrence of peripheral neuropathy. **Conclusion:** Patients with breast cancer receiving weekly paclitaxel also reported more PN if they had a vitamin D deficiency at baseline. This work adds to the growing body of data that vitamin D is a useful biomarker for predicting paclitaxel-induced peripheral neuropathy.

Keywords: Vitamin D, Peripheral Neuropathy, Paclitaxel, Breast cancer.

INTRODUCTION

Despite the growing number of cancer survivors, chemotherapy-induced peripheral neuropathy (CIPN) remains a prominent issue in oncological management. However, no standardized pathways exist to assess and manage [1].

Within 3 months of completing chemotherapy, 60% of patients are projected to have CIPN, and 30% of patients still have CIPN after 6 months. Unfortunately, even after 1–3 years of treatment, 11–80% of survivors may still experience CIPN-related discomforts during their follow-ups [2].

In the fight against breast cancer treatment, paclitaxel has proven to be a beneficial chemotherapeutic drug. Adjuvant therapy typically includes weekly administration of 80 mg/m2 for 12 weeks in cases with early-stage breast cancer. Early in the course of treatment, patients receiving weekly paclitaxel may

experience both subjective and objective neuropathy. Reducing the dose does not continually improve neuropathy symptoms [3].

About 25% of patients taking weekly paclitaxel experience PN of grade 2 or higher, and 10% of those patients experience PN symptoms for more than two years after treatment has ended, according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) grading scale [4]. Minimizing PN-related patient suffering, maintaining the integrity of paclitaxel treatment, and improving treatment efficacy would all be possible using a predictive, easily modifiable biomarker of PN [5].

However, the correlation between baseline nutritional deficits and paclitaxel-induced PN is poorly understood and may be a modifiable prognostic biomarker [6]; vitamin D deficiency is associated with an increased risk of PN in people with chronic alcohol use and diabetes [7].

Although this deficiency has been linked to PN regardless of its cause, its relevance as a risk factor for chemo-induced PN remains unclear. According to case reports, patients with vitamin D deficiency may benefit from supplementation for chemotherapy-induced peripheral neuropathy [8,9].

We hypothesized that Vitamin D deficiency could increase the severity of chemotherapy-induced peripheral neuropathy, so this study aimed to examine the correlations between Vitamin D level before therapy and PN severity during weekly paclitaxel treatment.

METHODS

This prospective study was performed at the medical Oncology department in Zagazig University Hospitals from August 2020 to March 2022. This prospective study analyzed data from 38 women enrolled in an observational cohort to receive sequential weekly adjuvant paclitaxel for breast cancer. After (AC) Anthracyclines (Doxorubicin), cyclophosphamide (Endoxan) based chemotherapy, patients had HER2 enriched, luminal b HER2 positive received both paclitaxel and trastuzumab (Herceptin) monoclonal antibody against HER2.

Inclusion criteria: Female patients who received paclitaxel 80 mg/m2 weekly for 12 weeks for stages I-III

Exclusion criteria: We excluded all who had any of the following conditions: Females with Stage IV breast cancer patients who have preexisting peripheral neuropathy from any cause. e.g., diabetes mellitus and chronic alcoholism, patients who experienced prior exposure to neurotoxic chemotherapy, women who were pregnant or nursing were not allowed to take part, nor were those who were using any of the following medications: platelet aggregation inhibitors, anticoagulants, anticonvulsants, opioids, medicines for neuropathic pain or tricyclic antidepressants., male breast cancer.

This study followed the guidelines [the World Medical Association's Code of Ethics (Declaration of Helsinki) for human studies]. All participants provided informed and written consent. The Institutional Review Board has approved this research (#6358/24-8-2020).

All patients had a treatment plan of Paclitaxel 80 mg/m2 as an adjuvant once weekly for 12 weeks.

Assessment of peripheral neuropathy: Patients filled out the EORTC Quality of Life Questionnaire, developed by the European Organization for the Research and Treatment of Cancer. Peripheral neuropathy caused by chemotherapy (CIPN20) before starting chemotherapy and then weekly during chemotherapy, the primary and secondary analyses relied on the entire scale, namely its 8-item sensory subscale (CIPN8). Each time point's raw CIPN8 score ranges from 8 to 32, as determined by adding the raw scores from all eight elements. To better reflect the severity of PN, the raw CIPN8 values were transformed into a linear scale running from 0 to 100, as suggested by the EORTC. Without access to the CIPN20 surveys, clinicians could not base treatment decisions on that data [1].

There are many pitfalls in grading severity of chemotherapy induced PN, as it is subjective assessment depend on patients described symptoms, so we added NCV for better assessment, CIPN was assessed by Adapted NCI CTCAE VERSION 6, as it was an easy and common which we used in our practice [10].

Neurophysiologic evaluation: A nerve conduction study (NCS) was conducted for all participants twice: before initiation and after termination of paclitaxel treatment. NCS was performed at the neurology outpatient clinic at Zagazig University Hospitals.

On the morning of the first paclitaxel infusion (to identify the serum level of vitamin D (base line level) before starting), blood samples were taken for baseline evaluation of nutrients associated with neuropathy before treatment began, Vitamin D deficiency was considered when (serum 25-OH-D levels < 20 ng/mL), insufficient 20-30ng/ml, normal>30 ng/ml. [3].

STATISTICAL ANALYSIS

Data analysis was performed using the software SPSS (Statistical Package for the Social Sciences) version 26. Absolute frequencies were used to define categorical variables, and the chi-square and Monte Carlo tests were used to compare them. The chi-square for trend test was performed to examine the relationship between the two sets of ordinal data. Parametric test assumptions were checked using the Shapiro-Wilk test. Means and standard deviations were used to characterize quantitative variables. One-way analysis of variance (for normally distributed data) was used to compare quantitative data from more than two groups. Spearman rank correlation coefficients (for non-normally distributed data) were used to evaluate the degree and direction of correlation between two continuous variables. The optimal cutoff value for a quantitative parameter utilized in the diagnosis of a health issue was determined using a receiver operating characteristic (ROC) curve.

RESULTS

This study included 38 patients with breast cancer. The participants reported no PN; 23 had a normal vitamin D level, 4 had insufficient vitamin D, and 11 had vitamin D deficiency at baseline. Patients were diagnosed at age range from 32 to 60 years with mean age 43.92 years. About 92% had T2. positive ER, PR, HER 2 and high Ki 67 prevailed in 71.1%, 44.7%, 71.1%, and 42.1% of patients respectively (cut off value of Ki we used is 14%). Concerning molecular type, 42.1% had luminal A, 21.1% had HER2 enriched, and 23.7% had luminal B/HER2 negative. About 71% of them were postmenopausal. Pre-menopausal females used IUD as contraceptive method. Only one patient (2.6%) had positive family history. About 58% had right side lesion. Body mass index ranged from 22.83 to 43.5 kg/m^2 with mean 33.21 kg/m^2 (Table 1).

There was a statistically significant difference between the groups regarding sensory ulnar latency, amplitude, or velocity after treatment. On making a post-hoc least significance difference (LSD) comparison, the difference was significant between insufficiency and each other group (highest latency and lowest amplitude and velocity) ($p<0.001$); within the sufficiency group, there was a significant increase in latency and non-significant change in amplitude or velocity ($p<0.001$), There was a statistically significant difference between the studied groups regarding sensory sural latency, amplitude, and sensory sural velocity after treatment ($p<0.001$ for each). On doing a post-hoc LSD comparison, the difference between insufficiency and sufficiency groups is significant. Within each group, there was a significant change in amplitude, latency, and velocity. (Table 2).

A statistically significant relation existed between vitamin D level and sensory nerve affection ($p<0.001$). Affected sensory nerves occurred in 63.6%, 100%, and 8.7% within deficiency, insufficiency, and sufficiency groups, respectively. Both sural and ulnar nerves were affected in 63.6% within the deficiency group versus 50% within the insufficiency groups and 8.7% within the sufficiency groups, respectively (Table 3).

A statistically significant relation existed between vitamin D level and motor nerve affection ($p=0.011$). Affected motor nerves occurred in 45.5%, 100%, and 8.7% within deficiency, insufficiency, and sufficiency groups, respectively (Table 4). There was a significant relation between groups regarding type and grade of peripheral neuropathy ($p<0.001$) (Table 3).

Our study included 38 patients all of them base line didn't experienced any degree of PN Despite some of them had base line vitamin D, Deficiency, Insufficiency after 12 weeks of adjuvant paclitaxel 80 mg/m,there was statistically non-significant relation between vitamin D level and incidence of peripheral neuropathy (100% within insufficiency and deficiency groups versus 21.7% within sufficiency group) while there was significant relation between groups regarding type and grade of peripheral neuropathy (Table 4).

There was a statistically significant positive correlation between vitamin D level after treatment and sensory ulnar velocity ($p=0.016$), sensory sural amplitude($p=0.02$), velocity($p=0.001$), peroneal ankle amplitude($p=0.001$), peroneal below fibula

head amplitude (0.034), velocity (p=0.004) and motor ulnar velocity (0.032). There was a significant negative correlation between vitamin D after treatment and all sensory sural latency(p=0.002) and peroneal ankle latency (p=0.002) after treatment (Table 5).

With an area under the curve of 0.864, specificity of 83.3%, sensitivity of 80%, positive predictive value of 84.2%, negative predictive value of 78.9%, and overall accuracy of 81.6%, a vitamin D cutoff of 30.75 ng/ml is found to be the most effective in predicting the incidence of peripheral neuropathy (Table 6 and Figure 1).

Table1: Distribution of studied patients according to baseline and disease specific data:

	Mean ± SD	Range
Age at diagnosis	43.92 ± 7.67	32 – 60
BMI (kg/m^2)	33.21 ± 4.25	23.83 – 43.5
	N=38	%
Type of surgery		
BCS	6	15.8%
MRM	32	84.2%
Pathology (IDC)	38	100%
Focality:		
Unifocal	37	97.4%
Multicentric	1	2.6%
Paget disease	1	2.6%
Negative surgical margin	38	100%
Negative LVI	38	100%
Tumor grade:		
G2	26	68.4%
G3	12	31.6%
T stage		
1	3	7.9%
2	35	92.1%
Axillary lymph node:		
N0	2	5.3%
N1	8	21.1%
N2	25	65.8%
N3	3	7.9%
M stage (0)	38	100%
Stage:		
2A	3	7.9%
2B	7	18.4%
3A	25	65.8%
3C	3	7.9%
Positive ER	27	71.1%
Positive PR	17	44.7%
Positive HER2	27	71.1%
High Ki67	16	42.1%
Molecular type:		
HER2 enriched	8	21.1%
Luminal A	16	42.1%
Luminal B/HER2 negative	9	23.7%
Luminal B/HER2 positive	2	5.3%
Triple negative	3	7.9%
Menopause:		

Pre **Post**	11 27	28.9% 71.1%
Contraception **IUD**	N=11 11	 100%
Hypertension	12	31.6%
Normal lt ventricular ejection fraction>55%.	38	100%
Positive family history	1	2.6%
Side: **Right** **Left**	 22 16	 57.9% 42.1%

BCS: Breast-conserving surgery, ER:Estrogen Receptors, PgR:Progesterone receptor, IDC: Infiltrating ductal carcinomas, HER2: Human epidermal receptor 2, LVI: Lymph vascular invasion, IUD: Intra uterine device, MRM: Modified radical mastectomy, G: Grade, N: Axillary lymph node

Table (2) Comparison between the studied groups regarding nerve conduction study of sensory division of ulnar nerve and nerve conduction of sural nerve before and after treatment

	Deficiency	**Insufficiency**	**Sufficiency**	**F**	**p**
	Mean ± SD	**Mean ± SD**	**Mean ± SD**		
Sensory ulnar latency pre	2.88 ± 0.24	3.0 ± 0.12	2.86 ± 0.22	0.753	0.478
Sensory ulnar latency post	2.89 ± 0.21	5.1 ± 2.37	2.97 ± 0.11	16.625	<0.001**
LSD comparison	P_1 <0.001**	P_2 <0.001**	P_3 0.764		
p¥	0.756	0.19	0.002*		
Sensory ulnar amplitude pre	17.3 ± 0.29	17.18 ± 0.22	17.3 ± 0.32	0.321	0.727
Sensory ulnar amplitude post	17.26 ± 0.27	12.33 ± 6.2	17.31 ± 0.28	13.136	<0.001**
LSD comparison	P_1 <0.001**	P_2 <0.001**	P_3 0.947		
p¥	0.459	0.225	0.892		
Sensory ulnar velocity pre	51.02 ± 1.3	52.58 ± 2.26	52.07 ± 1.81	1.807	0.179
Sensory ulnar velocity post	50.83 ± 0.96	41.45 ± 10.93	52.07 ± 1.9	15.085	<0.001**
LSD comparison	P_1 <0.001**	P_2 <0.001**	P_3 0.348		
p¥	0.336	0.19	0.97		
	Deficiency	Insufficiency	Sufficiency	F	p
	Mean ± SD	**Mean ± SD**	**Mean ± SD**		
Sensory sural latency pre	4.3 ± 0.13	4.15 ± 0.13	4.16 ± 0.19	2.703	0.081
Sensory sural latency post	5.83 ± 1.26	7.38 ± 1.19	4.21 ± 0.14	38.112	<0.001**
LSD comparison	P_1 <0.001**	P_2 <0.001**	P_3 <0.001**		
p¥	**0.002***	**0.011***	**0.045***		
Sensory sural amplitude pre	6.33 ± 0.35	6.23 ± 0.13	6.34 ± 0.3	0.245	0.784
Sensory sural amplitude post	3.61 ± 2.13	2.05 ± 0.65	5.75 ± 1.61	15.25	<0.001**
LSD comparison	P_1 0.079	P_2 <0.001**	P_3 <0.001**		
p¥	**0.003***	**0.007***	**0.036***		
Sensory sural velocity pre	42.16 ± 2.27	43.83 ± 2.47	42.83 ± 2.68	0.657	0.525
Sensory sural velocity post	29.02 ± 11.66	23.25 ± 8.85	41.89 ± 3.2	19.089	<0.001**
LSD comparison	P_1 0.179	P_2 <0.001**	P_3 0.764		
p¥	**0.005***	**0.017***	**0.039***		

F One way ANOVA test p¥ paired sample t test LSD Least significant difference p1 difference between deficiency and insufficiency groups p2 difference between insufficiency and deficiency groups p3 difference

between deficiency and sufficiency groups *p<0.05 is statistically significant **p≤0.001 is statistically highly significant

Table (3) Relation between vitamin D level and peripheral neuropathy among studied patients:

	Deficiency N=11 (%)	Insufficiency N=4 (%)	Sufficiency N=23 (%)	χ^2	p
Sensory nerve affected **No** **Sural** **Sural&ulnar**	4 (36.4%) 0 (0%) 7 (63.6%)	0 (0%) 2 (50%) 2 (50%)	21 (91.3%) 0 (0%) 2 (8.7%)	MC	<0.001**
Sensory nerve affection **No** **Affected**	4 (36.4%) 7 (63.6%)	0 (0%) 4 (100%)	21 (91.3%) 2 (8.7%)	11.872	<0.001**
Motor nerve affection **Peroneal, ulnar** **Peroneal** **Ulnar** **Normal**	2 (18.2%) 3 (27.3%) 1 (9.1%) 5 (45.5%)	0 (0%) 0 (0%) 0 (0%) 4 (100%)	0 (0%) 2 (8.7%) 0 (0%) 21 (91.3%)	MC	0.079
Motor nerve affection **Affected** **Not affected**	5 (45.5%) 6 (54.5%)	4 (100%) 0 (0%)	2 (8.7%) 21 (91.3%)	6.567	0.011*

MC Monte Carlo test χ^2Chi square for trend test **p≤0.001 is statistically highly significant

Table (4) Relation between vitamin D level and peripheral neuropathy among studied patients:

	Deficiency N=11 (%)	Insufficiency N=4 (%)	Sufficiency N=23 (%)	χ^2	p
PN post: **Grade 1 lower extremity motor** **Grade 1 lower extremity sensory** **Grade 1 lower extremity motor and sensory** **Grade 2 lower extremity motor** **Grade 2 lower extremity sensory** **Grade 2 lower extremity motor and sensory** **Grade 2 upper extremity motor** **Grade 2 upper& lower extremity motor** **Grade 2 upper& lower extremity sensory** **Normal**	0 (0%) 0 (0%) 0 (0%) 2 (18.2%) 4 (36.4%) 2 (18.2%) 1 (9.1%) 2 (18.2%) 0 (0%) 0 (0%)	0 (0%) 0 (0%) 0 (0%) 1 (25%) 1 (25%) 0 (0%) 0 (0%) 0 (0%) 2 (50%) 0 (%)	1 (4.3%) 3 (13%) 1 (4.3%) 0 (0%) 0 (0%) 0 (0%) 0 (0%) 0 (0%) 0 (0%) 18 (78.3%)	MC	<0.001**
PN post **Absent** **Present**	0 (0%) 11 (100%)	0 (0%) 4 (100%)	18 (78.3%) 5 (21.7%)	3.301	0.069

MC Monte Carlo test χ^2Chi square for trend test **p≤0.001 is statistically highly significant

Table (5) Correlation between vitamin D after treatment and nerve conduction study after treatment:

After treatment	r	p
Sensory ulnar latency	0.102	0.543
Sensory ulnar amplitude	0.135	0.418
Sensory ulnar velocity	**0.39**	**0.016***
Sensory sural latency	**-0.492**	**0.002***
Sensory sural amplitude	**0.376**	**0.02***
Sensory sural velocity	**0.505**	**0.001****
Motor peroneal ankle latency	**-0.482**	**0.002***
Motor peroneal ankle amplitude	**0.534**	**0.001****
Motor peroneal ankle velocity	0.107	0.523
Motor peroneal below fibula latency	-0.215	0.195
Motor peroneal below fibula amplitude	**0.344**	**0.034***
Motor peroneal below fibula velocity	**0.461**	**0.004***
Motor ulnar latency	-0.196	0.238
Motor ulnar amplitude	0.291	0.076
Motor ulnar velocity	**0.348**	**0.032***

r Spearman rank correlation coefficient *p<0.05 is statistically significant **p≤0.001 is statistically highly significant

Table (6) Performance of vitamin D in prediction of peripheral neuropathy among studied patients:

Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy	p
≤30.75	0.864	80%	83.3%	84.2%	78.9%	81.6%	<0.001**

AUC area under curve PPV positive predictive value NPV negative predictive value.

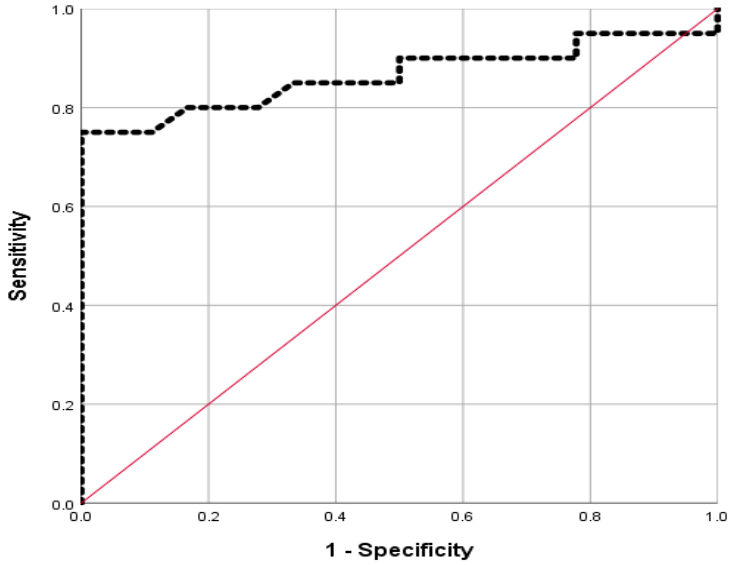

Figure (1) ROC curve showing Performance of vitamin D in prediction of peripheral neuropathy among studied patients

DISCUSSION

Breast cancer (BC) is the most common type of cancer among women. Breast cancer accounts for 29% of all cancer diagnoses in women and 14% of all cancer deaths, making it the second deadliest form of cancer in women after lung cancer. The incidence of male breast cancer is estimated to be around 1%, with most cases (90%) being characterized as estrogen receptor (ER)-positive [11].

Low serum vitamin D levels have been related to increased PN and neurotoxicity in aging and other diseases, such as immune-mediated PNs and other autoimmune disorders. However, the mechanism linking these phenomena is unclear. Despite vitamin D deficiency being associated with increased PN across these various sources, it is unclear if it is a risk factor for chemotherapy induced PN [12].

This study included 38 patients with breast cancer. All of them were non-alcoholic, non-diabetics, and non-pregnant non-smoker with normal left ventricular ejection fraction. About 71% of them were postmenopausal. Pre-menopausal females used the intra uterine device (IUD) as a contraceptive method. Only one patient (2.6%) had positive family history of cancer. About 58% had right-side lesions. Patients were diagnosed at ages 32 to 60 years, with a mean age of 43.92. Six patients underwent breast conservative surgery.

Similarly, **Zemlin et al. [13]** found that between September 2019 and January 2021, 110 women without metastatic breast cancer took part in the BEGYN research. The average age of the patients was 54 (range 26-81). Bilateral breast cancer affected 5 persons (4.5%). Ninety-four patients were diagnosed with cancer for the first time, accounting for 85.5%; 16 patients, or 14.5%, had a recurrence or second cancer. There was a 26 of body mass index (BMI) median (range: 19-39). Median pack-years of smoking experience was 17 (range, 1-58), and 42 patients (38.1%) were current or former smokers. Of the 201 patients surveyed, 101 reported drinking moderate alcohol (91.6 percent).

This study found that all patients had invasive duct carcinoma, negative surgical margin, and LVI with no distant metastasis. A more significant percentage had unifocal lesions. One patient had Paget disease, 68.4% had tumor grade 2, 65.8% had stage 3A, and 65.8% had N2 axillary lymph node invasion. About 92% had T stage 2 positive ER, PR, HER 2, and high Ki 67 >14 prevailed in 84.2%, 65.8%, 36.8%, and 44.7% of patients, respectively. Concerning molecular type, 42.1% had luminal A, 21.1% had HER2 enriched, and 23.7% had luminal B/HER2 negative.

Similarly, **Puspitaningtyas et al. [14]** found that most patients (115; 84.6% of total) were diagnosed with ductal infiltrative breast cancer, which is characterized by a lack of histological distinction (82, 60.3 percent). Most of the women in this study had locally advanced breast cancer (60, 44.1 percent). The immunohistochemical profiles of the individuals showed that a more significant percentage of the subjects had negative HER2 expression and positive ER and PR expression (81, 59.6%, and 69.5%, respectively) (90, 66.2 percent).

This study demonstrated a highly significant difference according to PN observed after paclitaxel treatment ($p < 0.05$).

Consistent with our findings, **Reyes-Gibby et al. [15]** found that many paclitaxel-previously-treated breast cancer survivors experienced discomfort severe enough to necessitate medical intervention. Twenty-five percent of people surveyed said they received medical attention for pain, with an average of two visits to their doctor or clinic in the preceding year (SD = 5). Only 27% said they relied on prescription painkillers, while 46.5% relied on over the counter (OTC) pain relievers. They compared neuropathic pain (NP) patients to non-NP patients to see if there were any differences in the frequency with which they saw their doctor and the use of medication for pain management, and they discovered that NP patients saw their doctor twice as often as non-NP patients (P =.028). Additionally, 50% of NP patients reported utilizing prescription pain medication, while only 19% of non-NP patients did so (P .0001). Most patients (62%), but not as many (45%; P =.086), have used OTC pain relievers.

In contradiction to our results, in **Bao et al. [16]** study, most patients receiving weekly paclitaxel chemotherapy experienced only minor CIPN and did not need treatment, indicating that future trials of CIPN prevention should target only those patients at high risk for the side effect.

This study illustrated a statistically significant relation between vitamin D level and sensory nerve affection. Affected sensory nerves occurred in 63.6%, 100%, and 8.7% within deficiency,

insufficiency, and sufficiency groups, respectively. Both sural and ulnar nerves were affected in 63.6% within the deficiency group versus 50% within the insufficiency groups and 8.7% within the sufficiency groups, respectively.

Abdelsadek et al. [17] used the neuropathy disability scale (NDS) and neurophysiological studies. They found an inverse correlation between PN severity and serum 25(OH) vitamin D levels, supporting our findings (peroneal motor nerve amplitude, sural sensory nerve amplitude, median sensory nerve amplitude, and sural sensory nerve conduction velocity; p 0.001).

Similarly, after 8 weeks of vitamin D therapy, **Akyuz et al. [18]** monitored Electromyographic (EMG) activity in individuals with chronic generalized pain. They found a significant improvement in sensory amplitudes of the sural and ulnar nerves.

Also, **Oraby et al. [19]** found that Nerve conduction studies (NCS) were performed on all patients, revealing a substantial correlation between the various serum vitamin D levels and the median nerve, ulnar nerve, tibial nerve, peroneal nerve, and sural nerve.

In this study, we uncovered a statistically significant relation between vitamin D level and motor nerve affection. Affected motor nerves occurred in 45.5%, 100%, and 8.7% within deficiency, insufficiency, and sufficiency groups, respectively.

Higher distal latency values were seen in the vitamin D-deficient category, and a significant association between vitamin D deficiency and ulnar nerve distal latency (p=0.024) was found by Gökhan et al. [20].

Also, **Abbas et al. [21]** found that after receiving paclitaxel, patients saw significant reductions in sensory (sural and superior peroneal nerve), motor (peroneal and tibial nerve), and distal (sural nerve) latencies, as well as amplitude and conduction velocity.

This is in concordance with the animal studies of **Nickander and colleagues. [22]** who found that Motor peroneal nerve conduction abnormalities were generated or exacerbated by vitamin D deficiency (ankle).

Also, **Kuru et al. [23]** found that Hypovitaminosis D was associated with delayed ulnar motor and left tibial motor latencies, as well as increased amplitudes in the motor nerve, evoked potentials (NCSs) of the median and ulnar nerves on both sides and the left tibia. Motor nerve conduction rates in the left ulnar and right peroneal areas also dropped significantly.

This study found a significant relationship between vitamin D levels and type and grade of peripheral neuropathy.

Yildirim and Cengiz[24] supported our results, where they found that Most patients had low levels of vitamin D, especially those who progressed to G2-G3 neuropathy. This is the first demonstration of a link between oxaliplatin-induced peripheral neuropathy (OIPN) and vitamin D, one of the best predictors of G2-G3 neuropathy.

In a recent case–control study by **Grim et al. [25],** pre-treatment vitamin D levels were lower in individuals who developed PN from paclitaxel (38.2 nmol/L vs. 25.6 nmol/L, p=0.008).

In addition, **He et al. [26]** discovered that low vitamin D levels are linked to PN, with a group of 16.01 ng/mL predicting a greater than 2-fold increase in the likelihood of developing DPN.

In addition, **Esteghamati et al. [27]** found that individuals with vitamin D deficiency (20 ng/mL) were more likely to develop symptomatic PN than those with a 25-OH-D level of 30-40 ng/mL (OR = 2.04, 95 percent CI = 0.99-4.02).

Against our study, **Kanbayashi et al. [28]** reported that Adjuvants and vitamin D used to treat PIPN-related symptoms during chemotherapy were not adequate, and a low vitamin D level within normal ranges was not found to be a predictor of worsening PN due to chemotherapy.

This study demonstrated a statistically significant positive correlation between vitamin D level after treatment and sensory ulnar velocity, sensory sural amplitude, velocity, peroneal ankle amplitude, peroneal below fibula head amplitude, velocity, and motor ulnar velocity. There were significant negative correlations between vitamin D after treatment, sensory sural latency, and peroneal ankle latency after treatment.

Assy et al. [29] corroborated our findings by showing an inverse relationship between vitamin D

levels and neuropathy scores, such that when vitamin D levels decreased, so did neuropathy scores (r = -0.325, p 0.05).

Similar results **Yildirim and Cengiz. [24]** shown in a retrospective study of patients treated with oxaliplatin for gastrointestinal cancer. Patients who went on to develop CIPN had significantly lower mean vitamin D levels at baseline than those who did not (17.2 ± 11.4 vs. 10.2± 7.2, p 0.001). According to a multivariate logistic regression analysis, vitamin D status was a significant (p 0.001) predictor of CIPN severity levels 2 and 3.

In this study, we revealed statistically non-significant relations between the incidence of peripheral neuropathy and age at diagnosis, menopause, family history, hypertension, type of surgery, side of the lesion, and focality.

Similarly, **Mielke et al. [30]** suggested that older cancer patients were not at increased risk for developing PN due to treatment (CIPN). This latter study likewise found that there was no correlation between age and CIPN severity.

Also, **Gaballah et al. [31]** found that neither younger nor older patients were more likely to develop CIPN (46.6% in those younger than 60 versus 48.8% in those more aged than 60; p = 0.781). There was no correlation between HTN and a worse CIPN severity score (p = 0.064).

With an area under the curve of 0.864, specificity of 83%, sensitivity of 80%, positive predictive value of 84%, negative predictive value of 79%, and overall accuracy of 81.6% (p0.001), we determined that a vitamin D cutoff of 30.75 ng/ml is the most effective for predicting the I of incidence peripheral neuropathy.

Our findings that vitamin D is only a protective factor for PN were supported by ROC analysis, which showed a cut-point value of 34.87 nmol/L (Youden index 0.20; sensitivity 70.01 percent; specificity 50.00 percent), with an area under the curve (AUC) of 0.614 (P.001), 95 percent CI: 0.565-0.663 (P.001).

Additionally, **Pang et al. [32]** observed that vitamin D deficiency (30 nmol/L) was associated with an increase in PN-related neurological impairments (paraesthesia, prickling, aberrant temperature, ankle hyporeflexia, and distal pall hypoesthesia; Y = 0.005306X + 2.105, P = 0.048).

limitations & recommendations

Among the limitations of the study were a small sample size. Further study with larger sample size is essential to establish our results, we recommend to include also cases of metastatic breast cancer, to provide vitamin D supplement to the affected group and analysis the result of improvement of PN in them after correction level by NCV not only clinical assessment, up till now no proved medication to treat paclitaxel induced PN, so we hope that positivity of our study to help in provide therapy to the affected group, also we recommend to screen all patient received paclitaxel as part of their protocol regimen for vitamin D level ,and to provide vitamin D supplement in patients who had had insufficiency or deficiency.

CONCLUSION

We found that individuals with breast cancer receiving weekly paclitaxel who were vitamin D deficient at baseline were more likely to get PN. Vitamin D is a predictive biomarker of paclitaxel-induced PN, and this study's findings contribute to the expanding body of evidence favoring this hypothesis.

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